Bull. Org. mond. Santé
Bull. Wld Hlth Org. } 1966, **34**, 357-361

Ocular Manifestations of Vitamin-A Deficiency in Man*

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Vitamin-A deficiency continues to be one of the most widely prevalent and devastating nutritional diseases of man. This is in spite of the discovery of vitamin A more than half a century ago and its now ready availability in inexpensive concentrated form. Lack of knowledge at many levels is the basis of this tragic situation, which may result in needless blindness and loss of life, especially among young children.

As a contribution to the alleviation of the problem, the present paper has as its object the provision, for the general and hospital physician in those countries where xerophthalmia is endemic, of adequate descriptive and pictorial information to enable him to make an accurate diagnosis of vitamin-A deficiency when he is presented with any stage of the ocular manifestations.

In recent years there has been increasing recognition of the widespread occurrence of vitamin-A deficiency in man (Oomen, 1961; McLaren, 1963). In its most serious form not only is sight threatened, frequently resulting in total blindness, but there is also a high mortality (McLaren et al., 1965). The pre-school child, more particularly between the ages of nine months and four years, is especially at risk. In many countries vitamin-A deficiency is the major cause of blindness in this age-group.

The ocular manifestations of vitamin-A deficiency merit special attention, not only because the destructive corneal lesions lead to permanent impairment of vision, but also because they afford, in man, the only reliable clinical evidence of the deficiency state. Moreover, serum levels of the vitamin in individuals do not correlate well with eye changes indicative of early vitamin-A deficiency.

When a single descriptive clinical term was sought for this disease entity it seemed that "xerophthalmia" was the best available. This word has the advantages of long and general usage together with the implication of a serious affection of the eyes. Although etymologically only eye involvement is implied, in common medical parlance an advanced state of generalized hypovitaminosis A is understood. It is therefore suggested that the more specific terms "conjunctival xerosis" and "corneal xerosis" be used in describing the actual state of the eye itself and that "xerophthalmia" be reserved for the syndrome.

There are several reasons why xerophthalmia has hitherto not received the attention it merits. It is only in the past 30 years or so that protein malnutrition, with which xerophthalmia is more commonly than not associated, has come to be recognized as one of the most prevalent and serious of all diseases. Concentration on protein malnutrition has led to the neglect of other aspects of malnutrition in the child, and xerophthalmia has suffered particularly in this regard. In the countries where xerophthalmia is common—all of them having few doctors and most of them over-populated—there are but a handful of physicians who have received special training in the examination of the eye. After all, physicians in general feel diffident about passing an opinion on a lesion affecting such a specialized organ as the eye. Unfortunately ophthalmologists tend to be preoccupied with surgery and feel, perhaps not altogether unnaturally, that a condition that is often almost hopeless when they first see the case lies

* This investigation was supported by the World Health Organization and by United States Public Health Service Research Grants NIH AM 06735 to the World Health Organization and AM 05285 to the Institute of Nutrition Sciences, Columbia University, New York.

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outside their province. Even the parents may not have their attention attracted to the condition until it is too late and the corneas are dissolving away behind the closed eyelids of the young child. Finally the high mortality, even in xerophthalmia cases treated in hospital, reduces the social consequences of blindness and further contributes to the neglect of the problem.

During 1962-63, WHO implemented recommendations that had been made by several Joint FAO/WHO Expert Committees and undertook a global survey of xerophthalmia. The epidemiological and public health aspects were surveyed in nearly 50 countries in South and East Asia, the Eastern Mediterranean, North Africa, and Central and South America (Oomen, McLaren & Escapini, 1964).

The present paper is the result of many years' experience of each one of the authors in countries where the xerophthalmia problem exists, together with the accumulated knowledge of many other physicians in all these countries. Our objective is to provide the practising physician with clear descriptions and illustrations of the eye lesions of vitamin-A deficiency so that he may recognize the condition in all its stages.

In view of the common occurrence of eye involvement in malnourished children, it needs to be reiterated that the eyes should always be fully examined and their condition carefully noted in reports of protein malnutrition (McLaren, 1958). Furthermore, there is now evidence to show that, even in the absence of overt physical changes in the eye, the liver stores of vitamin A in the protein-malnourished child are usually very low (McLaren et al., 1965). Consequently, restoration of these stores should be part of any regime of rehabilitation of these children.

THE POSTERIOR SEGMENT OF THE EYE

Rod function

Diminution in the supply of vitamin A in the form of the aldehyde (retinene, retinal) to the rod cells of the retina results in impairment of the function of dark adaptation. This may be detected by rod scotometry (Livingston, 1944), dark adaptometry (Hume & Krebs, 1949), and electroretinography (Dhanda, 1955) long before the subject complains of night-blindness. Unfortunately, all these methods are not applicable to the susceptible age-group—the pre-school child—because a fully co-operative and intelligent subject is essential. They also require expensive and delicate equipment not suitable for field studies. The development of a simple yet sensitive objective biophysical test of rod function applicable to population groups susceptible to vitamin-A deficiency would be a distinct advance in measuring the extent of the problem.

The symptom of night-blindness should always suggest the possibility of vitamin-A deficiency, but it may result from non-nutritional causes, such as congenital night-blindness and retinitis pigmentosa.

The optic fundus

Several reports from East Asia have described changes in the fundus resembling those seen in retinitis punctata albescens and which, it is claimed, respond to vitamin-A therapy. Teng Khoen Hing (1959, 1964) has reported many cases in Indonesia and has published fundus photographs. The possibility that factors other than nutrition are responsible has to be entertained, for such changes have not been found associated with vitamin-A deficiency elsewhere (Halasa & McLaren, 1964).

THE ANTERIOR SEGMENT OF THE EYE

Conjunctival appearances

The changes characteristic of vitamin-A deficiency are usually confined to the bulbar conjunctiva, but occasionally in long-standing cases the conjunctiva of the lower lid and adjacent lower fornix may be rough and wrinkled.

Conjunctival xerosis (Plate IA, D and Plate IIA, B, C). This may be generalized throughout the exposed part of the bulbar conjunctiva or localized to a small part or parts of the same. Whatever the extent of the changes, their nature is the same and has the following characteristics:

(*a*) Dryness—the literal meaning of "xerosis". Dryness is judged by lack of the normal lustre or brilliance of the bulbar conjunctiva. The appearance has been likened to that of wax or dry paint.

(*b*) "Unwettability". This occurs regardless of the presence or absence of tears. Patches of xerosis emerge from their surroundings "like sandbanks at receding tide" when the child stops crying. This probably results from the disruption of the continuity of the preconjunctival film by the xerotic process in the epithelium.

(*c*) Loss of transparency. The ability of the conjunctiva to transmit light is impaired, leading to decreased visibility of the conjunctival vessels. On

inspection with the slit-lamp, the translucent conjunctiva, which normally looks clear ("like an aquarium") and crossed by blood vessels, appears to be milky owing to fine droplets. Soon the vascular pattern, apart from the large arterioles, becomes obscured.

(*d*) Thickening. There is a tendency to generalized thickening and stiffness of the conjunctiva.

(*e*) Wrinkling. There are small, more or less vertical folds in the conjunctiva best demonstrated by rucking up the loose temporal conjunctiva against the outer canthus on maximal lateral movement of the eyeball.

(*f*) Pigmentation. In dark-skinned races there is a fine, diffuse smoky pigmentation, which is not to be confused with the patchy and coarser pigmentation that is frequently observed in healthy subjects of these races. In prolonged xerosis, the lower fornix first becomes yellowish, then light grey and finally dark brown owing to the presence of chromatophores in the basal cell layer of the epithelium. This characteristic "gutter" pigmentation responds slowly, over a period of weeks or months, to treatment.

Bitot's spot (Plate IB, Plate IIA, B, C, and Plate IV). The usual form taken by a Bitot's spot is a small plaque of a silvery-grey hue with a foamy surface. It is quite superficial and is raised above the general level of the conjunctiva; it is more or less readily removed by manipulation of the lids or direct wiping, revealing a xerotic conjunctival bed with a rough surface.

Bitot's spot is invariably situated on the bulbar conjunctiva, frequently bilateral and temporal and less commonly nasal, and is usually confined to the interpalpebral fissure close to the limbus. This typical location of the spot would seem to be explained by the protection of the material here from the wiping movements of the lids, close to the protruding limbus. The shape varies considerably, being often irregularly circular or oval with the long axis horizontal. The classical triangular form with the base to the limbus is less common.

Exceptionally, the following variations may be found. Bitot's spot material may be scattered widely over the conjunctiva, sometimes having a vertically corrugated arrangement. Not all spots are foamy; some have a cheese-like or grease-like surface. Some accumulations are quite exuberant and not flat like a plaque. The significance of these differences in appearance is not known. The spots may be black in children whose eyelids are smeared with mascara (e.g., *kajal* in India, a mixture of carbon and grease). If an unusual part of the conjunctiva is permanently exposed, as in strabismus, coloboma of the eyelid, or ectropion, a Bitot's spot may develop in relation to such an area, illustrating the etiological importance of exposure.

Bitot's spot may or may not be associated with generalized conjunctival xerosis. When so associated, the subjects are usually young children and may also have night blindness. These spots, together with the accompanying generalized xerosis, usually respond to vitamin-A therapy. Bitot's spots are also encountered in some parts of the world without generalized xerosis or evidence of retinal dysfunction, usually in older children and adults. These are often minimal lesions; evidence of vitamin-A deficiency may be lacking (Plate IID), and there may be no response to therapy (Darby et al., 1960; Paton & McLaren, 1960).

Accumulation of debris (Plate IC and Plate IIIA). In some cases of advanced xerosis, debris accumulates on the surface of the bulbar conjunctiva and may spread on to the adjacent part of the cornea. This material is creamy white, glistening, non-foamy and easily becomes detached to lie in the canthi, the lower fornix, or on the eyelid borders. This is a quite unusual appearance, Bitot's spot being much more common. The material of the latter adheres more tenaciously to the eye.

Any one, or even several, of these appearances may not be taken as diagnostic of conjunctival xerosis due to vitamin-A deficiency. The presence of most or all of them is highly suggestive of such a diagnosis, which will be confirmed by a return to the normal appearance under adequate therapy. Bitot's spot is a useful indicator of vitamin-A deficiency, especially in young children, but it is not pathognomonic.

Corneal changes

Active stages. These lead on from the appearances of conjunctival xerosis, which are in evidence by the time the cornea has become affected. Both corneas usually show changes but to widely varying degrees. Photophobia and inflammatory changes are not regarded as essential features. In the uncomplicated case, the mildness of congestion in the eye is truly remarkable.

Reversible changes (Plate ID) are characterized by generalized corneal xerosis, dryness, "unwettability" and loss of transparency, which lead to an early haziness of the cornea. These appearances

may be demonstrated by holding the lids apart for 15 seconds. Slit-lamp examination at this early stage may reveal an increase of fine pigment in the paralimbal portions of the cornea, although it must be remembered that pigment in this area is common in healthy members of darkly pigmented races. There may also be a loss of continuity of the surface epithelium and diminished tactile sensitivity. Later, cellular infiltration of the corneal stroma contributes to the intensity of the haziness of the cornea, which frequently has a bluish, milky appearance, usually most marked in the lower central part. In some cases there is a cellular exudate in the lower part of the anterior chamber.

Irreversible changes are characterized by the following signs:

(*a*) " Ulceration ", (Plate IE) which involves a loss of substance of a part or the whole of the corneal thickness. This phenomenon is designated " ulceration " for lack of a more specific term, but it is characterized by mild signs of reaction or inflammation. Advanced degrees of stromal loss result in descemetocele and complete perforation with iris prolapse. These lesions are more common in the lower central cornea.

(*b*) Keratomalacia (Plate IF and Plate IIIB), which consists of a characteristic softening (colliquative necrosis) of the entire thickness of a part, or more often the whole, of the cornea, invariably leading to deformation or destruction of the eyeball. The process is a rapid one, the corneal structure melting into a cloudy gelatinous mass which may be dead-white or dirty-yellowish in colour. Extrusion of the lens and loss of vitreous may occur. In untreated cases, endophthalmitis not infrequently supervenes. Particularly in very young children, keratomalacia may rapidly develop in the absence of the characteristic changes, described earlier, in the conjunctiva.

Sequelae (Plate IIIC). These result from the spontaneous or therapy-assisted healing of the irreversible changes mentioned above. The least serious as to vision are nebulae and small leucomata situated away from the pupillary area, usually in the lower central part of the cornea. If the iris has prolapsed there will be leucoma adherens with distortion of the pupil. Large, often heavily vascularized and pigmented, total or subtotal leucomata cause loss of vision, fortunately often affecting only one eye with minimal changes in the other.

Keratomalacia, on healing, results in anterior staphyloma composed of the scarred remnant of the cornea and incorporated elements of uvea bulging forwards under the influence of raised intra-ocular pressure. If the damaged cornea ruptures rather than bulges then the contents are extruded, and a shrunken globe, phthisis bulbi, is the end result.

ACKNOWLEDGEMENT

We are grateful to members of Nutrition and of Communicable Diseases, WHO, Geneva, for helpful discussions.

RÉSUMÉ

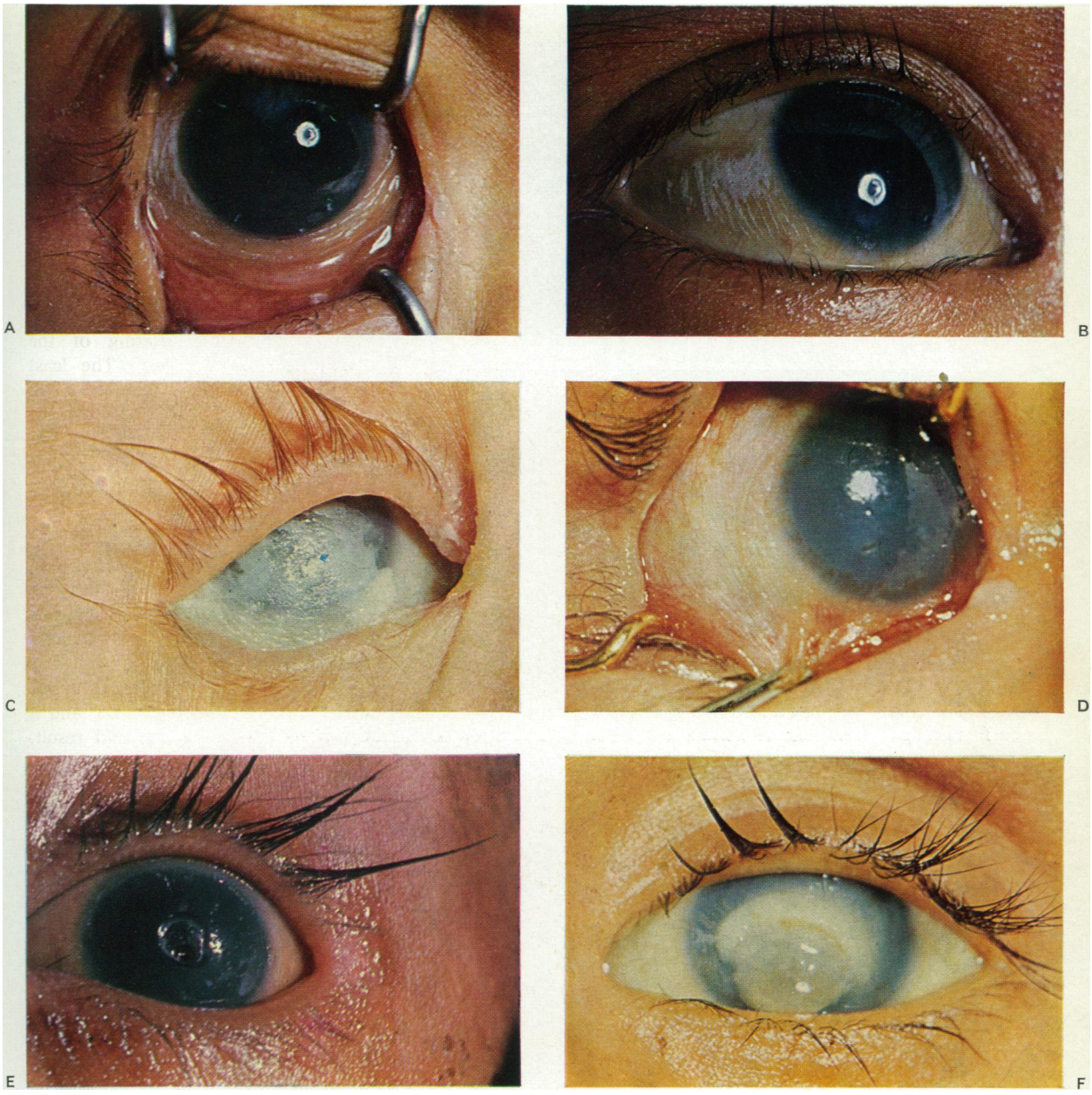
Les manifestations oculaires de l'hypovitaminose A revêtent une importance particulière en raison de leur fréquente gravité et aussi parce qu'elles sont le seul indice clinique sûr d'une telle carence.

Un apport insuffisant de vitamine A aux tissus rétiniens entraîne une détérioration de la fonction d'adaptation à l'obscurité. Les différentes méthodes destinées à objectiver ces troubles requièrent malheureusement la collaboration du sujet examiné et ne peuvent servir au dépistage de la carence dans le groupe, spécialement vulnérable, des enfants d'âge préscolaire.

Les premiers signes cliniques apparaissent au niveau du segment antérieur de l'œil et consistent généralement en lésions de la conjonctive bulbaire. Celle-ci perd son film protecteur, devient sèche, moins transparente; elle s'épaissit, se plisse et présente une légère pigmentation. L'existence éventuelle d'une tache de Bitot, de forme et d'étendue très variables, peut poser un problème étiologique: souvent associée à d'autres signes d'hypovitaminose A, elle peut cependant exister en l'absence de toute carence et de toute atteinte rétinienne et résister au traitement par la vitamine A.

Au niveau de la cornée, les lésions sont de deux ordres. Certaines, réversibles en cas de traitement précoce, ont un caractère nettement évolutif. Elles succèdent aux altérations pathologiques de la conjonctive et sont du même type. Si la carence est notable, l'évolution s'accélère et les lésions irréversibles apparaissent rapidement, surtout chez les jeunes enfants: ulcération grave de la cornée, perte de substance suivie de cicatrisation ou de perfora-

PLATE I



A. Extensive xerosis of the conjunctiva with oedematous folds in the lower conjunctival sac. Distorted Bitot's spot visible. Male Indonesian child aged 4 years, right eye. Tests revealed blood-plasma vitamin-A level of 3 μg/100 ml, and a trace of carotene.

B. Bitot's spot, striated, with hyperpigmentation and dryness of surrounding conjunctiva. Male Indonesian child aged 3 years, right eye.

C. Accumulation of debris in a 9-month-old Jordanian male infant. The material has extended from the lower fornix on to the greater part of the cornea. Tests revealed blood-plasma vitamin-A level of 2 μg/100 ml and liver vitamin-A level of 0 μg/g liver.

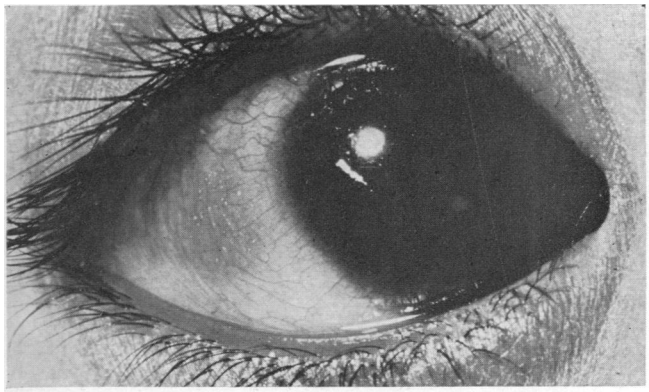
D. Haziness and infiltration of the cornea, with early neovascularization. Xerosis conjunctivae is also well shown. Male Jordanian child aged 2 years 3 months. Tests revealed blood-plasma vitamin-A level of 3 μg/100 ml and liver vitamin-A level of 0 μg/g liver.

E. Eye of Guatemalan infant showing central softening with ulcer formation. Reaction is minimal; scarring inevitable.

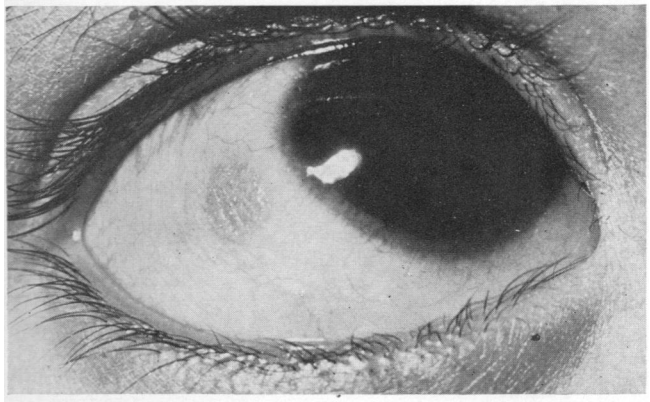
F. Perforation of the cornea and extrusion of the lens in an 18-month-old Jordanian male child. Tests revealed blood-plasma vitamin-A level of 2 μg/100 ml.

Comparative values for healthy children: plasma vitamin A 20-50 μg/100 ml; liver vitamin A 50 μg/g.

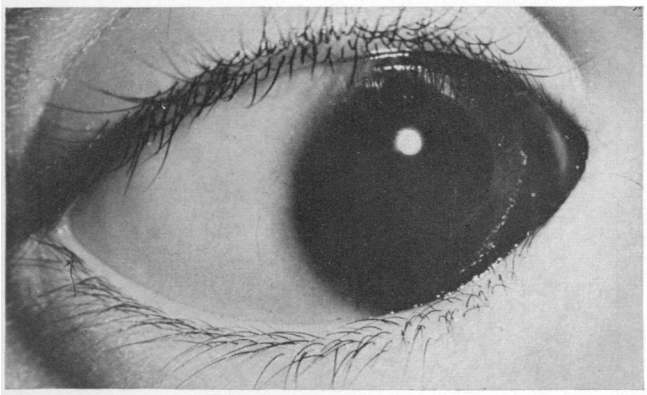
PLATE II



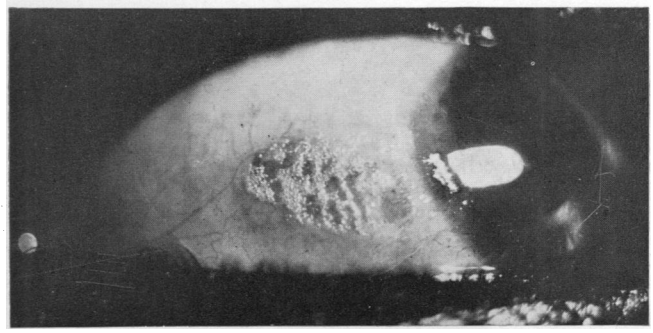
A. Generalized xerosis of the bulbar conjunctiva in a male Jordanian child aged 1 year 3 months before treatment. The conjunctiva is dry, thickened and wrinkled and lacks lustre. Centrally there is increased pigmentation and flecks of foamy Bitot's spot material. There is considerable conjunctival injection. Tests revealed blood-plasma vitamin-A level of 7 μg/100 ml and liver vitamin-A level of 5 μg/g liver.



B. Same eye as Plate IIA, 16 days later, after commencement of treatment with 10 000 international units of water-dispersible vitamin-A palmitate per kilogram of body weight daily for five days. There were no local applications. The peripheral conjunctiva is now clear, transparent and no longer wrinkled, and the injection has disappeared. The central pigmented area with Bitot's spot material now stands out in contrast. Tests showed blood-plasma vitamin-A level of 25 μg/100 ml.

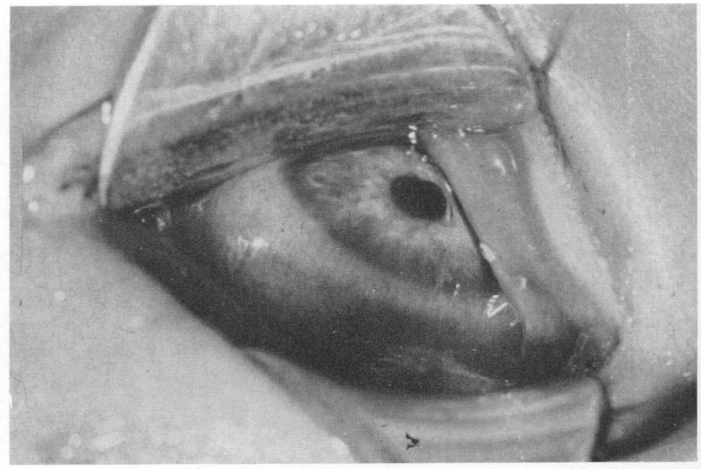


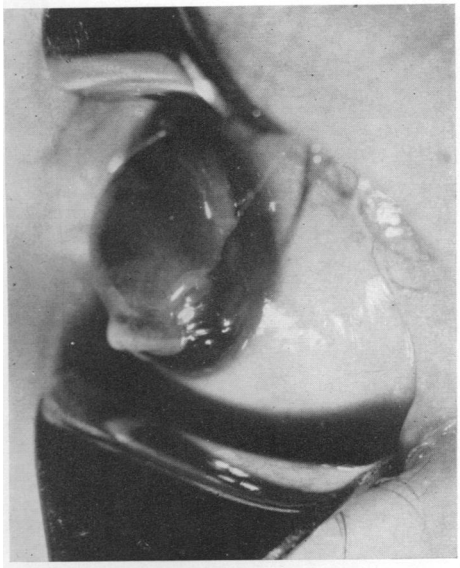
C. Same eye as Plate IIA and IIB, 29 days after commencement of treatment. No additional vitamin A was given apart from that in the regular hospital diet. Bulbar conjunctiva is now completely clear. Tests showed blood-plasma vitamin-A level of 7 μg/100 ml and liver vitamin-A level of 136 μg/g liver.



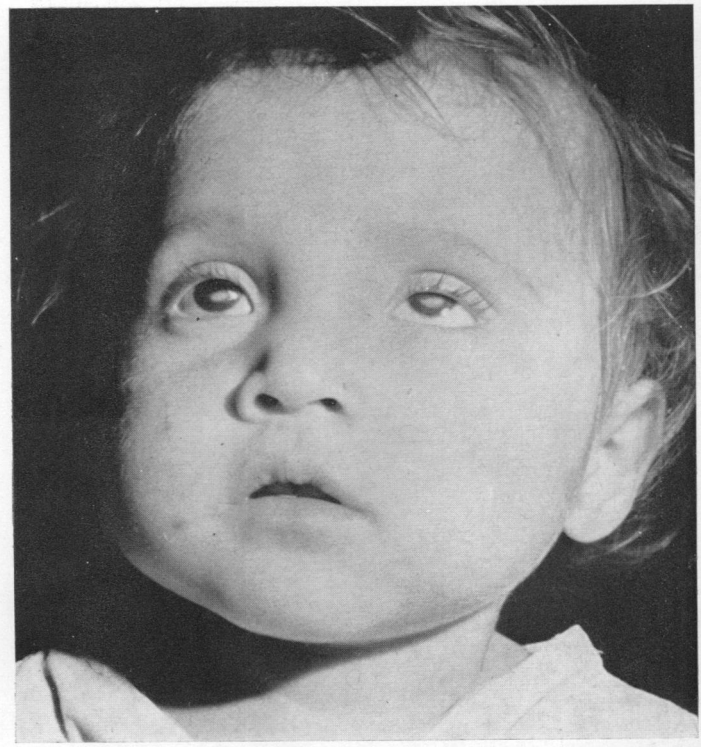
D. Bitot's spot in an Ethiopian male aged 10 years. This and many other similar cases have been studied carefully for evidence of vitamin-A deficiency and response to therapy. All results have been negative (Darby et al., 1960; Paton & McLaren, 1960). The Bitot spot is confined to the exposed part of the bulbar conjunctiva, the rest of the conjunctiva being normal.

A. Same eye as in Plate IC, seven days after treatment with an intramuscular administration of 50 000 international units of vitamin-A palmitate in oil per kilogram of body weight, given in one dose. Plasma vitamin-A level rose to 11 μg/100 ml. Debris completely cleared, revealing normal cornea.





B. Keratomalacia affecting entire cornea of Egyptian child aged 2 years. Absence of reaction and secondary infection is striking. Such eyes are not acutely painful, and consequently they are frequently neglected by the parents.

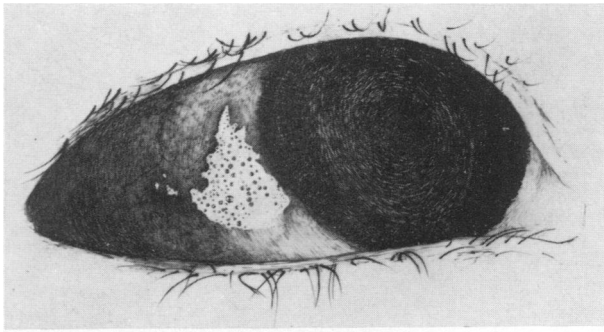


C. Bilateral scars of cornea in El Salvadorian child recovering in hospital from xerophthalmia and kwashiorkor. The situation of the scars in the lower central part of the cornea is characteristic. More advanced changes lead to phthisis bulbi or anterior staphyloma.

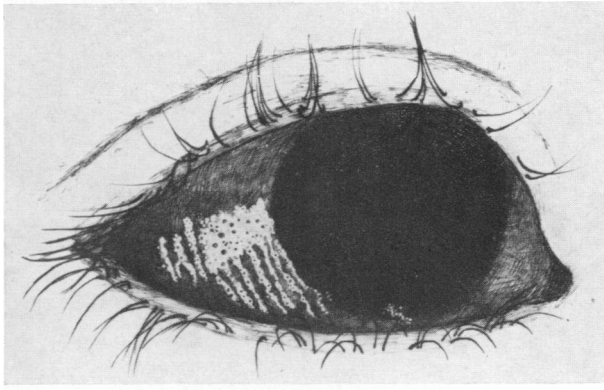
PLATE IV

BITOT'S SPOTS IN JAVANESE CHILDREN

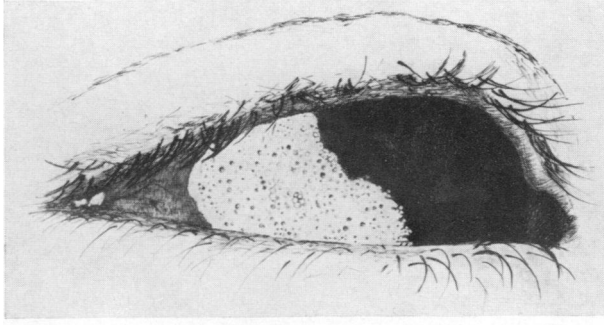
Ink drawings by H. Sterkman after colour macrophotographs



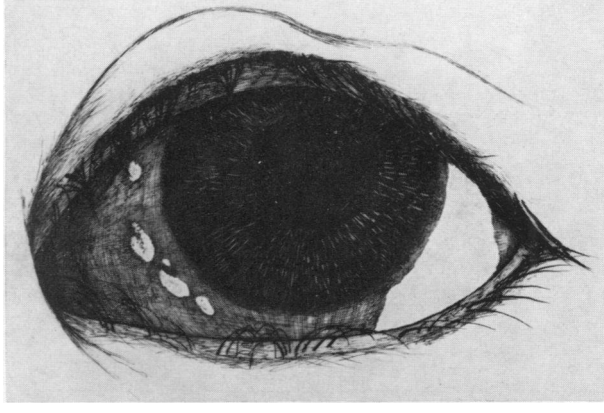
A. Circumscribed triangular lateral spot on a xerotic conjunctival patch in a 9-year-old girl.



B. Striated lateral spot in a 3-year-old boy.



C. Large lateral spot overflowing the limbus in a 22-month-old boy. The spot leaves only part of the exposed bulbar conjunctiva visible.



D. Large fluid lateral spot and four small medial spots in a 3-year-old boy.

tion avec iridocèle. Fréquemment, la cornée tout entière se nécrose et se liquéfie, présentant le tableau clinique de la kératomalacie.

Les séquelles, succédant aux lésions irréversibles, n'ont que peu d'importance fonctionnelle en cas de taie ou de leucome bénin n'intéressant pas l'aire pupillaire. Les leucomes plus étendus ou adhérents entraînent la perte de la vision de l'œil atteint. La kératomalacie, après guérison, laissera persister un staphylome antérieur ou un globe oculaire atrophié avec perte complète de la fonction.

En dépit de son étymologie, les auteurs préfèrent réserver le terme « xérophtalmie » à l'ensemble des manifestations cliniques dues aux formes graves de l'hypovitaminose A et utiliser, pour la description des lésions oculaires, une terminologie plus spécifique.

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